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This Month in Genetics

Kathryn B. Garber[1,*]

Population-Based Longitudinal Study of Autism in Sweden

In the largest study of its kind, Sandin et al. estimated heritability and familial risk of autism and autism spectrum disorder via a population-based Swedish sample. The sample totaled more than two million individuals who were born in Sweden between 1982 and 2006 and followed longitudinally through 2009. Because of a healthcare system with equal access, a mandatory developmental assessment of all 4-year-old children, and a country-wide, population-based register that allowed the researchers to connect family members, this study avoided many of the ascertainment-bias issues that could have skewed data from similar studies. The authors were also able to assess risk of autism on the basis of family relationships that ranged from twins to siblings to first cousins. The heritability estimated for autism spectrum disorder on the basis of these data was 0.5, substantially lower than what has been estimated by some prior studies.

Sandin et al. (2014). JAMA 311, 1770–1777.

Risk-Reduction Surgery in Women with *BRCA1* or *BRCA2* Mutations

In a recent analysis of data from an international registry of women with *BRCA1* or *BRCA2* mutations, the Hereditary Ovarian Cancer Clinical Study Group further illustrates the benefit of prophylactic oophorectomy in these women. The study included more than 5,000 mutation carriers who were followed for a mean of 5.6 years. Preventive removal of the ovaries resulted in an 80% reduction in risk of ovarian, peritoneal, or fallopian tube cancers, but it also resulted in a 77% reduction in risk of all-cause mortality. The authors use their data to provide guidance on the age at which the surgery should be recommended in women with *BRCA1* or *BRCA2* mutations, and on the basis of 18 occult fallopian tube cancers identified in women at the time of prophylactic surgery, they also argue for the removal of the fallopian tubes during the same surgery.

Finch et al. (2014). J. Clin. Oncol. 32, 1547–1553.

One Fell Swoop

The gene-by-gene approach or testing panels: which to use? Both strategies are now available for genetic testing of many heterogeneous conditions. One is tried and true, and the other gives you more bang for your buck. Providing data that might help this decision-making process for ordering physicians, Ambry Genetics has recently published its experience with four different hereditary cancer genetic testing panels of more than 2,000 patients. The fraction of cases considered positive ranged from 7.2% to 9.6% depending on the panel. In contrast, the fraction of cases with an inconclusive result ranged from 15.1% to 25.6%, and for the ovarian cancer panel, it was more than three times that of the positive rate for the same test. Not all genes on each panel conferred the same level of cancer risk. For both the overall cancer panel and the breast cancer panel, the genes in which pathogenic variants were most likely to be found were those such as *CHEK2* and *PALB2*, genes that appear to contribute a moderate increase in cancer risk and for which management guidelines for carriers and their families do not exist. Although not unexpected, these results illustrate some of the benefits and challenges of testing cancer-associated genes in one fell swoop.

LaDuca et al. (2014). Genet. Med. Published online April 24, 2014. http://dx.doi.org/10.1038/gim.2014.40.

Getting It Right

When interpreting sequence variation, we don't always get it right, despite our best efforts. Unfortunately, once these incorrect interpretations make it into databases and into the literature, they are propagated, often yielding false-positive results in which genes and individual variants are wrongly assumed to be causative for disease. When diagnostic labs, patients, and physicians use this information, there is the potential for harm. An expert working group assembled by the National Human Genome Research Institute provides their perspective on these issues in a recent *Nature* paper. They present their views on the types of evidence needed for concluding that a gene is relevant for a phenotype and those that are needed for interpreting a specific variant within a causative gene. At both the gene and variant levels, this working group argues for a more quantitative approach to sequence interpretation.

MacArthur et al. (2014). Nature 508, 469–476.

Reversal of Fortune

One of the common causes of mortality in individuals with the progressive disorder Friedreich ataxia (FA) is cardiomyopathy. Because adeno-associated virus (AAV) targets the heart when injected intravenously, Perdomini et al. wondered whether a gene therapy delivered via this route

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could change the course of the disease. In fact, it not only prevents cardiomyopathy in mice that are treated presymptomatically but also can reverse damage in mice that already have heart failure. The model they used lacked frataxin in the cardiac and skeletal muscle and caused a rapid and severe progression of cardiomyopathy, resulting in death at approximately 9 weeks of age. Injecting these mice at 3 weeks of age with an AAV-expressing human frataxin prevented development of cardiac disease and resulted in normal survival rates. Even more strikingly, when the gene therapy was delayed and given to mice with advanced cardiac insufficiency, the treatment reversed much of the heart damage, yielding rapid improvement in cardiac function and mitochondrial organization and prolonging survival. Although this vector didn't target all tissues affected by FA, the change in disease course in the mouse model is promising for future clinical trials.

Perdomini et al. (2014). Nat. Med. 20, 542–547.

This Month in Our Sister Journals

fastSTRUCTURE

One of the popular algorithms for identifying clusters of individuals on the basis of multilocus genotype information is STRUCTURE. This can be used, for example, for better understanding human population history and ferretting out population structure, which can be a problem for genome-wide association studies. As samples get bigger and our capacity for higher-throughput genotyping increases, the computational burden on methods such as STRUCTURE gets to be a problem. Raj, Stephens, and Pritchard have developed an efficient algorithm called fastSTRUCTURE, which uses a variational Bayesian framework. It is almost 100× faster than STRUCTURE and is able to infer ancestry with accuracy similar to that of other popular approaches to identifying population structure.

Raj et al. (2014). Genetics. Published online April 15, 2014. http://dx.doi.org/10.1534/genetics.114.164350.